

# migraine & serotonergic antagonists



# INTENDED LEARNING OBJECTIVES (ILO)



By the end of this lecture the student will be able to:

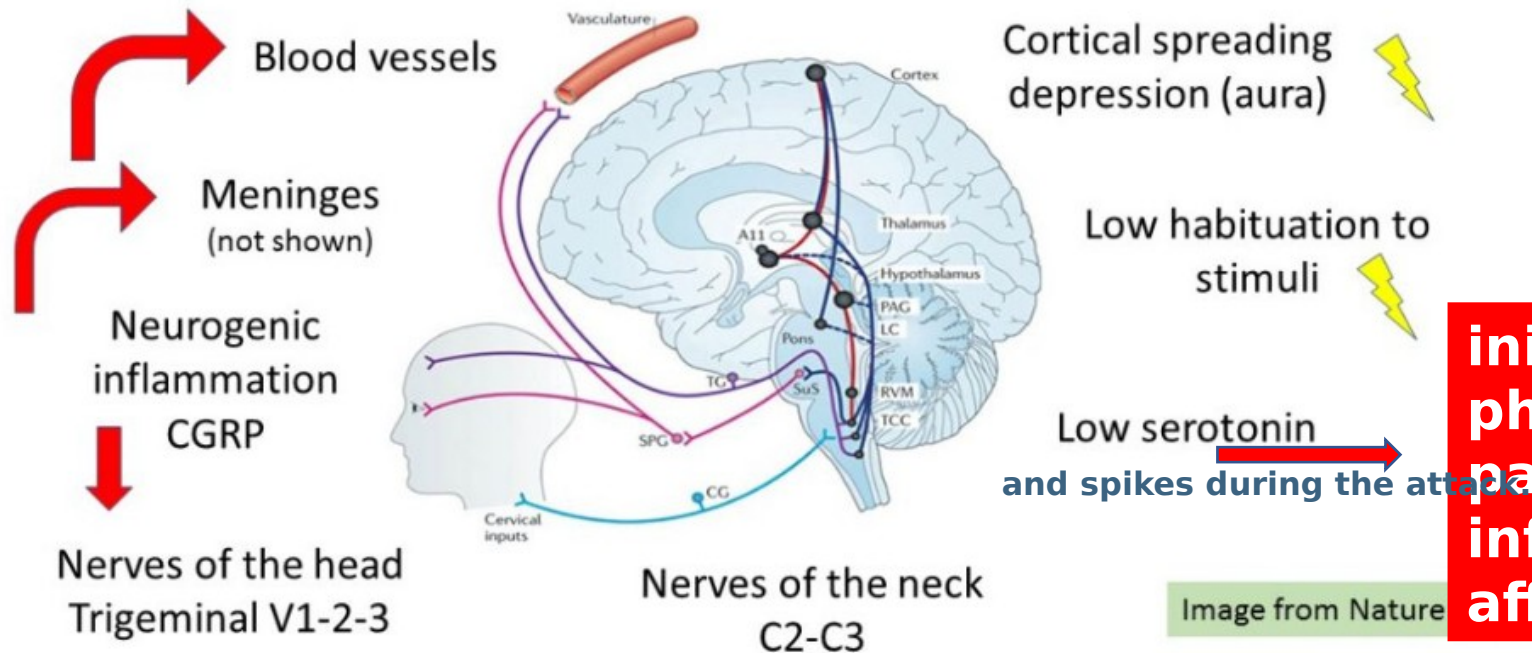
1. List the different lines of treating migraine .
2. Describe pharmacodynamics and kinetics of triptans and ergots.

# The cause of migraine

**Migraine is a neurological disease, and it has many different mechanisms. We cannot just say «X is the cause of migraine». We have to look at it like a puzzle with different pieces.**



# The puzzle of migraine pathophysiology



**initiate the vasoconstrictor phase of migraine & participate in neurogenic inflammation of the affected blood vessels.**

**All these pieces probably influenced by genes**

**migraine is not visible on CT scans and MRIs.**  
Migraine is like a software problem, where the computer still looks fine

# Serotonin (5HT)

- 90% of body's content of 5-HT is localized in the enterochromaffin cells of stomach and intestines; most of the rest is in platelets and brain. It is also found in scorpion sting, and is widely distributed in plants (banana, pear, pineapple, tomato, stinging nettle).

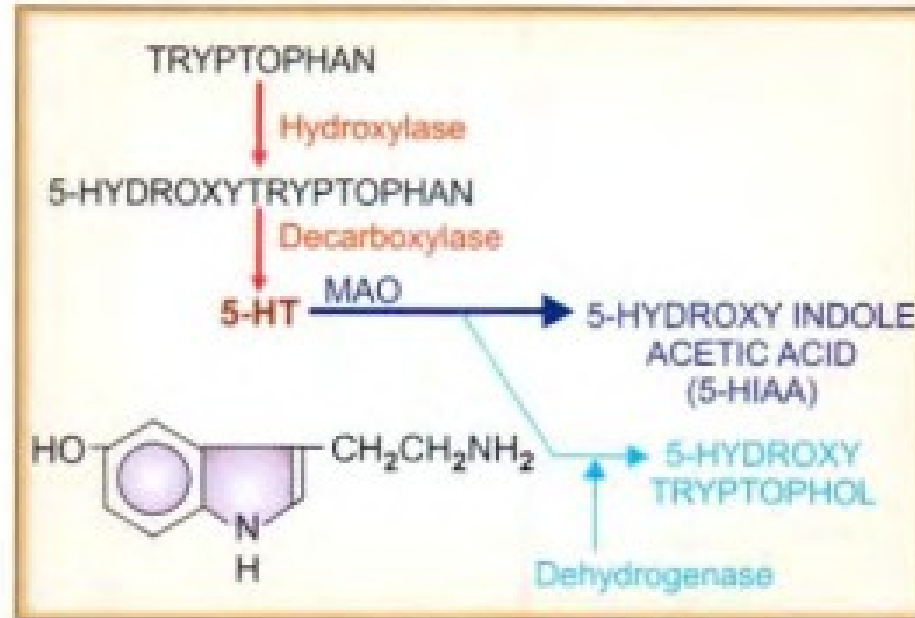


Fig. 12.1: Synthesis and degradation of 5-hydroxytryptamine (5-HT)

# Serotonin receptors

- Four families of 5-HT receptors (5-HT1, 5-HT2, 5-HT3, 5-HT4\_7) comprising of 14 receptor subtypes have so far been recognized.
- **5-HT3** is a ligand gated cation (Na<sup>-</sup>,K<sup>+</sup>) channel
- Other 5-HT receptors are G protein coupled receptors which function through **decreasing (5-HT1)** or **increasing (5-HT4, 5-HT6, 5-HT7)** cAMP production, or by generating IP/ DAG (5-HT2) as second messengers.

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# ACTIONS

- Arteries

- constricted (direct action)
- Dilated (through EDRF release) depending on the vascular bed and the basal tone.
- In addition, 5-HT releases Adrenaline from adrenal medulla
- The net effect is **complex**.
  - Larger arteries and veins are characteristically constricted.
  - In the microcirculation 5-HT dilates arterioles and constricts venules, capillary pressure rises and fluid escapes.

- Visceral smooth muscle:

- Peristalsis is increased **and diarrhea** can occur.
- **Constricts bronchi**.

- Glands:

- 5-HT inhibits gastric secretion (both acid and pepsin), but increases mucus production.

- Nerve ending

- + Afferent nerve endings → **tingling** and pricking sensation, as well as pain.

- CNS

- poor entry across blood-brain barrier.
- as a transmitter, primarily **inhibitory (sleepiness)**

# Pathophysiological Roles of serotonin

- As a neurotransmitter plays a role in anxiety, depression, aggression and other behavioral disorders in humans
- As a precursor of melatonin has a role in biological clock and maintain circadian rhythm
- Nausea and vomiting.
- Raynaud's phenomenon
- Variant angina
- Hypertension
- Carcinoid syndrome: ↑ ↑ ↑ 5-HT → Bowel hypermotility and bronchoconstriction but flushing and hypotension are probably caused by other mediators. Pellagra in carcinoid may occur due to diversion of tryptophan for synthesizing 5-HT.
- **Migraine**



# Drug acting on serotonin

## ERGOT ALKALOIDS

- Ergot is a fungus *Claviceps purpurea* which grows on rye, millet and some other grains
- Epidemics of ergot poisoning (**ergotism**), due to consumption of contaminated grains → **Painful dry gangrene** of hands and feet which become black (as if burnt) occurs due to vasospastic ischemia. Miscarriages occur in women and cattle.
- **Natural ergot alkaloids** contains compounds that divided into-
  - (a) Ergometrine : which is oxytocic.
  - (b) Ergotamine they are vasoconstrictor and alpha adrenergic blocker.
- **Semisynthetic derivatives:**
  - **Dihydroergotamine (DHE):** are antiadrenergic
  - **Bromocriptine:** is a dopaminergic D2 agonist
  - **Methysergide:** it is mainly anti 5-HT.

### Side effect:

- Nausea, vomiting, abdominal pain, muscle cramps, weakness, paresthesias,
- Coronary and other vascular spasm, chest pain (due to coronary vasoconstriction)

## Drug therapy of migraine



Severity	Drug therapy
Mild	: Simple analgesics/NSAIDs or their combinations ( $\pm$ antiemetic)
Moderate	: NSAIDs combinations/a triptan/ergot alkaloids (+ antiemetic)
Severe	: a Triptan/ergot alkaloids (+ antiemetic)
	+ Prophylaxis
	<ul style="list-style-type: none"><li>• Propranolol/other <math>\beta</math> blockers</li><li>• Amitriptyline/other tricyclic antidepressants</li><li>• Flunarizine/other <math>\text{Ca}^{2+}</math> channel blockers</li><li>• Valproate/topiramate</li></ul>

# Drug therapy of migraine

- **Mild migraine**

*???Cases having fewer than one attack per month*

- **Simple analgesic** like paracetamol
- **NSAIDs**
- **Combination:**
  - NSAIDs with paracetamol/codeine or antihistaminic (diphenhydramine)

**1<sup>st</sup> G antihistamines exert sedative as well as antiemetic action.**

# Drug therapy of migraine

## Moderate migraine when

- Throbbing headache is for 6-12 hours,
- nausea/vomiting are more prominent
- patient is functionally impaired

## Treatment guide

- Simple analgesics are usually not effective,
- **NSAIDs or their combinations** mentioned above are beneficial in many cases.
- The remaining **specific antimigraine drug**, i.e. a triptan or an ergot preparation.
- **Antiemetics** regularly needed.

Antiemetic added to relieve nausea, vomiting and gastric Stasis (Gastric stasis occurs during migraine which delays absorption of oral drugs).

*NB: When the patient has already vomited. it is better to give the antiemetic by injection (im).*

# Drug therapy of migraine

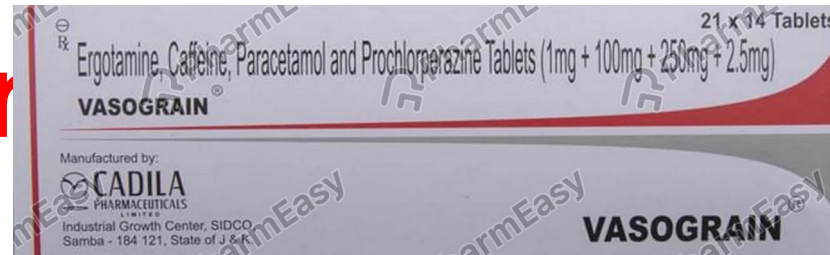
## **Severe migraine** when

- 2- 3 or more attacks per month
- Last >12 hours
- often accompanied by vertigo, vomiting
- incapacitated during the attack.

## **Treatment guide**

- **Specific antimigraine**
- **antiemetics.**
- **Combination of a longer acting analgesic like naproxen with a triptan**
- **Prophylactic regimens for attacks lasting 6 months or more are recommended.**

# Ergotamine



- It is the most effective ergot alkaloid for migraine.
- Oral-sublingual route (Parenteral administrations more hazardous)

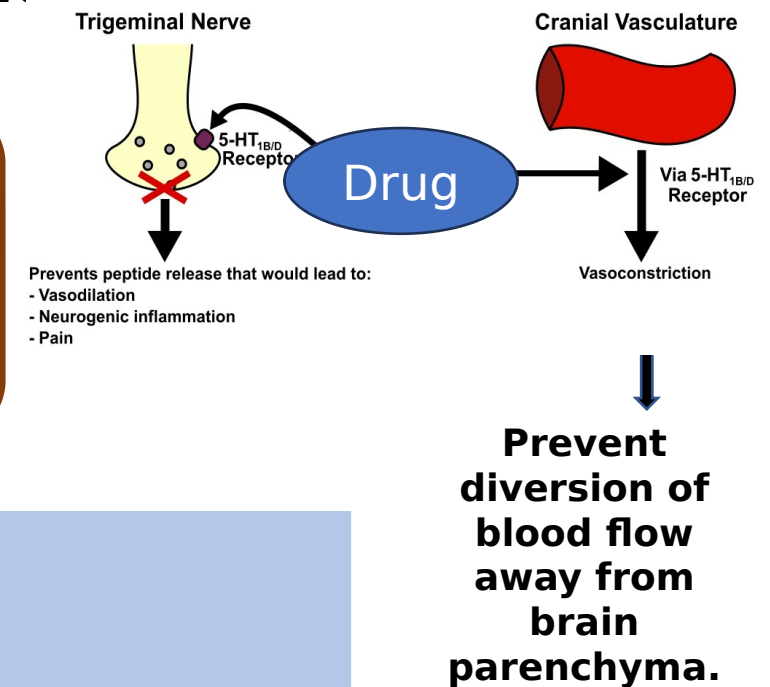
## Mechanism:

**partial agonism at 5-HT<sub>1B/1D</sub>**

- constricting the dilated cranial vessels.
- reduce neurogenic inflammation and leakage of plasma in dura mater

*Caffeine* 100 mg taken with ergotamine

- Enhances its absorption from oral and rectal routes
- adds to the cranial vasoconstricting action.



# Dihydroergotamine (DHE)

- **Dihydroergotamine (DHE)** It is nearly as effective as ergotamine and **preferred for parenteral administration** because injected DHE is less hazardous.



*Current status* Because of

- erratic oral absorption
- frequent side effects, especially nausea, vomiting, muscle cramps
- availability of triptans

Ergot preparations are rarely used now, except for considerations of cost or when triptans fail.

# Selective 5-HT<sub>1B/1D</sub> agonists (Triptans)

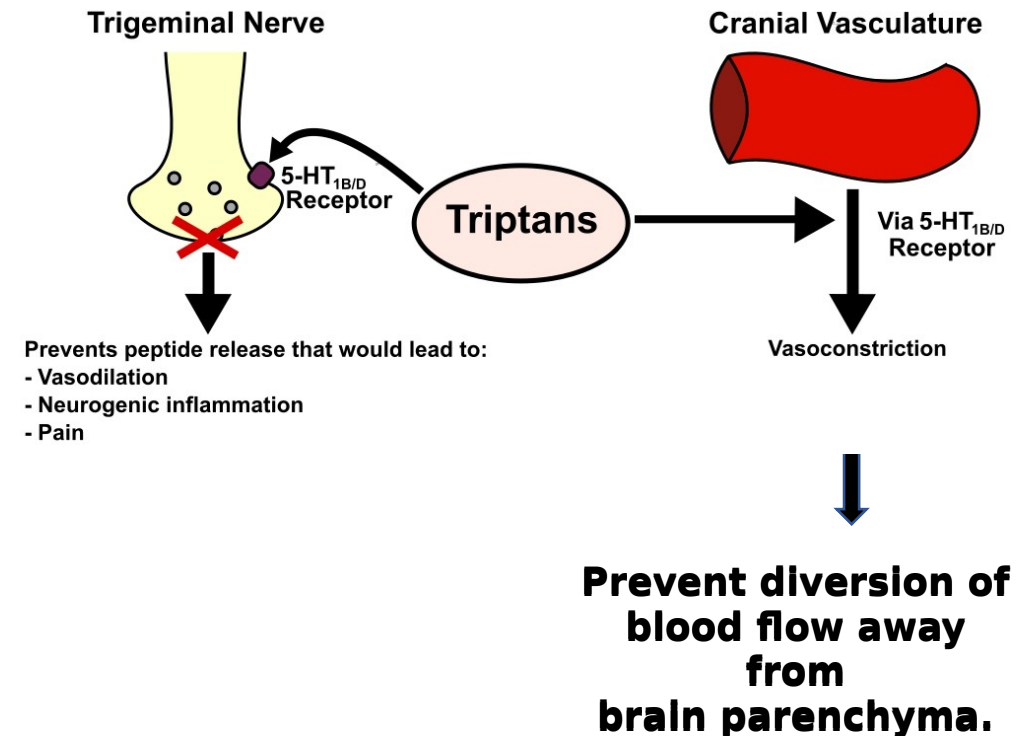
- **Sumatriptan** It is the first selective 5-HT<sub>1B/1D</sub> receptor agonist
- All others triptans have higher oral bioavailability.
- Naratriptan and frovatriptan
  - longer  $t_{1/2}$ ,
  - slower in onset





# Selective 5-HT<sub>1B/1D</sub> agonists (Triptans)

1. Constricts dilated cranial blood vessels, especially the arterio-venous shunts in the carotid artery, which express 5-HT<sub>1B/1D</sub> receptors.
2. inhibits inflammatory neuropeptide release around the affected vessels as well as extravasation of plasma proteins across dural vessels (presynaptic).



# Selective 5-HT<sub>1B/1D</sub> agonists (Triptans)- adverse effects

- usually mild, dose dependent, short lasting.

- Tightness in head and chest
- Feeling of heat
- paresthesias in limbs
- Dizziness,
- Weakness

are more common after  
s.c. injection, which is  
painful

## Rare but serious

- Bradycardia, coronary vasospasm.
- convulsion

**On BP:** Of no clinical value, it is  
not a drug for regular use.

# Selective 5-HT<sub>1B/1D</sub> agonists (Triptans)- contraindication and interactions

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- Coronary artery disease
- Hypertension
- Peripheral vascular disease
- Epilepsy, hepatic or renal impairment
- Pregnancy and Lactation

## Precautions:

- Avoid SSRI and TCA, MAOIs.....(serotonin syndrome)
- Sumatriptan and ergotamine should not be administered within 24 hours of each other.
- Should not be used for more than 2 days a week to decrease the possibility of rebound

# Recent

- **Ditans (Lasmiditan)**

5-HT<sub>1F</sub> receptor agonist for acute migraine treatment.

The utility of this medication is that it **lacks vasoconstrictor effects** and thus offers those with cardiovascular disease an alternative to triptans.

- **Calcitonin Gene-Related Peptide (CGRP) inhibitors**



# Calcitonin Gene-Related Peptide (CGRP) inhibitors

Two forms exists:

- monoclonal antibodies (erenumab)
- CGRP receptor antagonists (gepants).

Unlike monoclonal antibodies, gepants rapidly penetrate the brain so work quickly.



# PROPHYLAXIS OF MIGRAINE

- moderate-to-severe migraine when 2- 3 or more attacks occur per month,
- when attacks are disabling despite treatment

## Beta-Adrenergic blockers

- **Propranolol** is the **most commonly** used drug.
- nonselective (timolol)
- selective (metoprolol, atenolol)

But pindolol (intrinsic sympathomimetic action are not useful)

# PROPHYLAXIS OF MIGRAINE

## Tricyclic antidepressants

- This class of drugs are better suited for patients who concurrently suffer from depression.

## Calcium channel blockers

- **Verapamil**.
- **Flunarizine** is a relatively weak Ca channel blocker that inhibits Na<sup>+</sup> channels as well. Effective as propranolol



## Anticonvulsant

- **Topiramate** in refractory cases.

## CGRP antagonist

# Migraine in pregnancy

- **Ergotamine** is contraindicated during pregnancy and was in FDA category **X** under the prior pregnancy drug rating system.
- **NSAIDs** are not advised for use in the **third trimester** as they may increase the risk of prematurely closing the fetal ductus arteriosus.
- **Valproate** is contraindicated during pregnancy and was also in FDA category **X**.
- **First-trimester** exposure to **topiramate** correlates with cleft lip/palate. Topiramate was in FDA category D.



